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Try to treat Parkinson's like an old friend

As an 80-year-old with Parkinson's, how do you coax the best quality of life from your daily existence? A lifetime of experience and zest for life is showing Sheng Kanghua how.

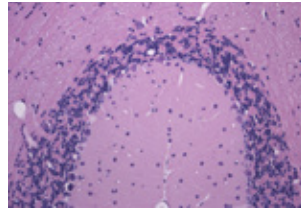


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The eyes follow her, unblinking

For a fearful child, a vivid fantasy world can be a refuge. It was for Ditte Grauen Larsen, who's now 26. But it also opened a door to a universe where eyes on the leaves of trees were watching her, and where reality was as slippery as a skating rink.



Visit the Lundbeck website
www.lundbeck.com

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This is Lundbeck

Today, millions of people all over the world live with depression, schizophrenia, Alzheimer's and Parkinson's diseases. At Lundbeck, we want to understand why these diseases occur and to develop the best treatments to help ease the symptoms or cure them completely.

Research into the brain is one of the costliest to undertake. Not only does it take longer, but it also has a higher failure rate than most other medical research. But with brain disorders sharply on the rise, it's more important than ever. Lundbeck is one of the only global pharmaceutical companies to focus exclusively on psychiatric and neurological disorders. By investing in research, we can discover and develop treatments that ease the burden of these disorders around the world.

For more than 70 years, we've been pushing the boundaries of neuroscience. By combining the logic of science with our passion for making a difference to patients, we've pioneered some of the most significant and commonly used therapies within antipsychotics and antidepressants. We work closely with patients, healthcare professionals and the neuroscience community to uncover causes and to find new treatments that can bring back quality of life to people living with brain disorders.

When most organs in our body get sick, we find compassion and care in people around us. But when our brain suffers, the world typically turns away. As a global specialist, we owe it

**"When most organs in our body get sick,
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those who live with psychiatric and neurological
disorders to fight stigma and promote
better treatment."**

to those who live with psychiatric and neurological disorders to fight stigma and promote better treatment. That's why we work to improve understanding and parity of care across communities and societies – so we can empower people and rebuild hope.

Today, we're a strong team of 5,000 people in more than 50 countries. We build on our Danish heritage, fostering a culture of collaboration and responsibility. Whether we work in labs or in the field, we all have the same aim: to develop innovative treatments that improve the lives of people with psychiatric and neurological disorders. We call this progress in mind.

In this year's Lundbeck Magazine, we feature four honest and moving patient stories from Sheng Kanghua, Enric Alvarez Guayta, Ruth Joseph and Ditte Grauen Larsen. I would like to thank them all for their courage and willingness to share their experiences. It is through their stories that we, as a company, get wiser and learn to understand our patients and their needs.

In addition, we have included a piece on our continuing fascination of the brain, along with stories that detail

how we are promoting sustainability in our business and our foundation ownership. You will also find a story on our extensive compound invention legacy and patient reach today, as well as features on key characteristics of our four focus diseases.

I hope you enjoy the stories in this year's magazine.



Anders Götzsche

Interim CEO and Executive Vice President, CFO

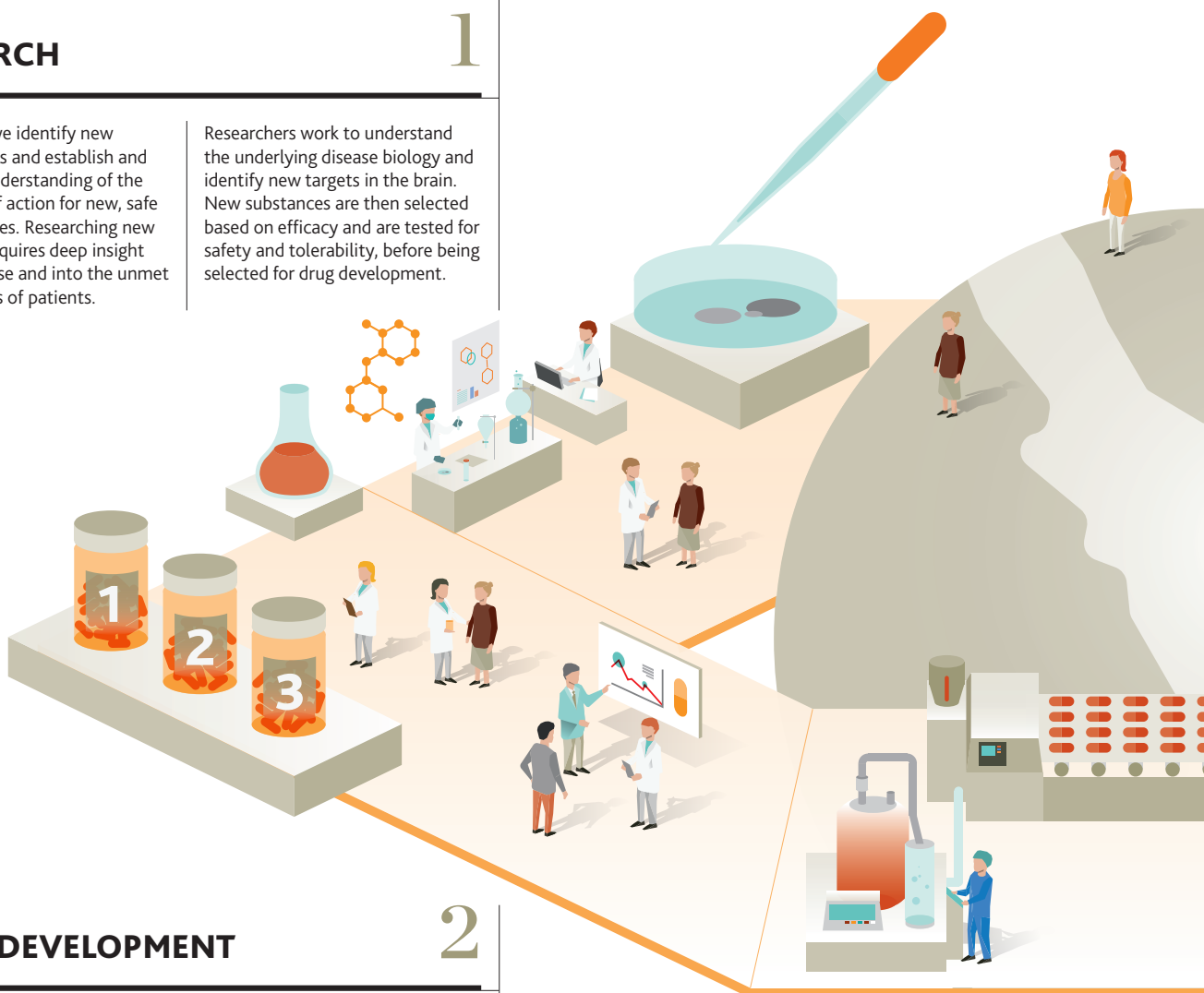
From idea to patient

RESEARCH

1

In Research, we identify new disease targets and establish and confirm an understanding of the mechanism of action for new, safe drug candidates. Researching new treatments requires deep insight into the disease and into the unmet medical needs of patients.

Researchers work to understand the underlying disease biology and identify new targets in the brain. New substances are then selected based on efficacy and are tested for safety and tolerability, before being selected for drug development.



DRUG DEVELOPMENT

2

In Drug Development, we conduct clinical studies globally to establish evidence for new drug candidates, we engage healthcare specialists in scientific discussions to enhance the understanding of our clinical

results, and we work to develop safe, reliable and efficient manufacturing processes. Safeguarding the rights, safety and well-being of study participants is of the greatest importance.

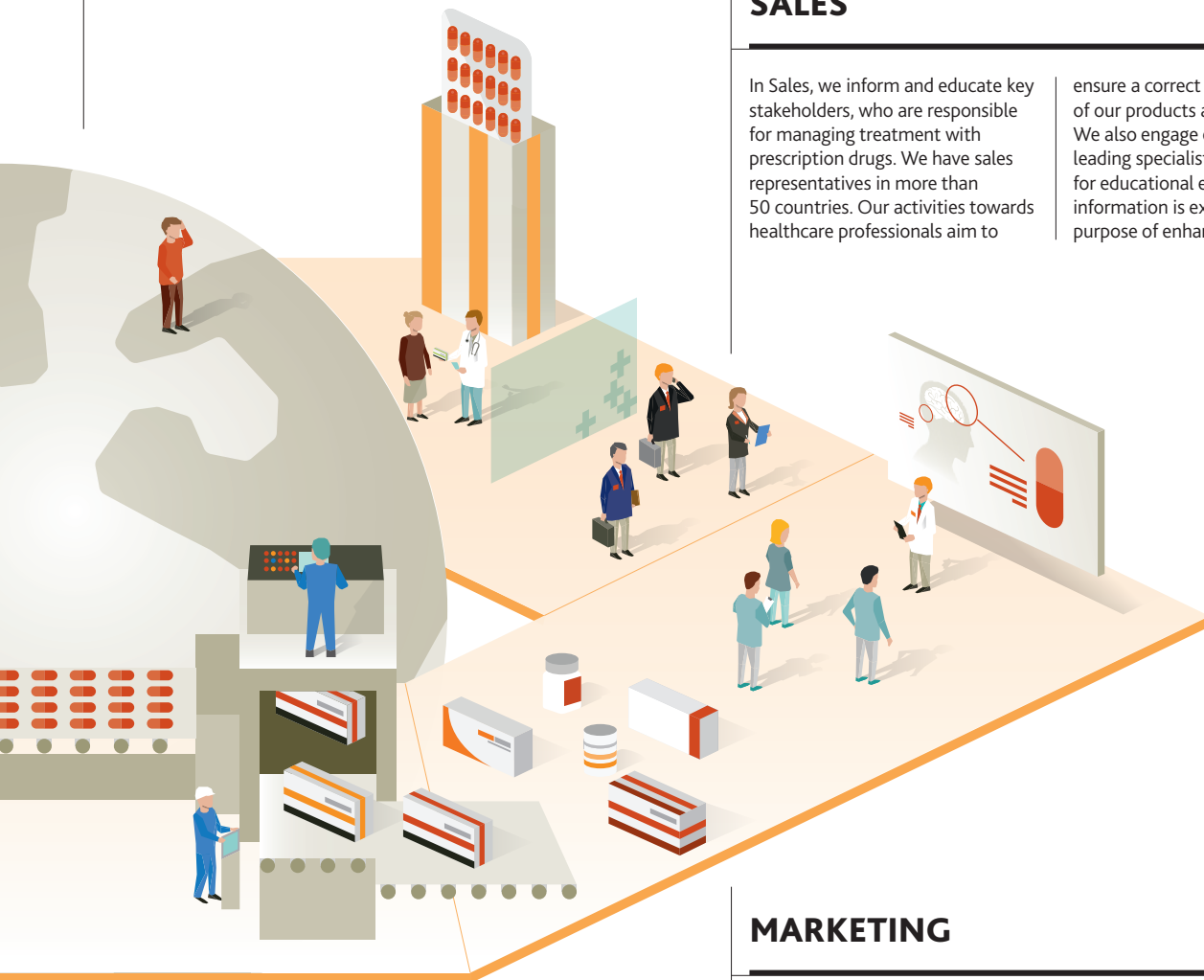
PRODUCTION

3

The production process has three major stages: Chemical Production where the active pharmaceutical ingredient is made; Pharmaceutical Bulk Production where the product is produced; and the Finished Goods Production where the packs are assembled. We strive to create the best supply chain in the

pharmaceutical industry through continuous improvement of reliability, quality and cost. Every year more than 100 million finished goods are sent to distributors, wholesalers and hospitals through close collaboration with our sales affiliates.

Developing innovative and safe treatments is complex. It takes approximately 10-15 years for a new drug to move through the pharmaceutical value chain from when an idea is conceived until an approved treatment is made available to patients.



SALES

5

In Sales, we inform and educate key stakeholders, who are responsible for managing treatment with prescription drugs. We have sales representatives in more than 50 countries. Our activities towards healthcare professionals aim to

ensure a correct understanding of our products and their use. We also engage experts and leading specialists as speakers for educational events, where information is exchanged with the purpose of enhancing patient care.

MARKETING

4

Our products are registered globally in more than 100 countries. We produce and conduct scientific and promotional events to educate HCPs about the safe and effective use of our products. We engage

decision-makers in activities to help them prioritize psychiatric and neurological disorders and argue the societal value of our products based on thorough assessments.

Mr Alzheimer is waiting in the street

The sicker Enric Álvarez Guayta gets, the healthier he feels. To him, Alzheimer's is primarily a menacing figure who lies in wait down on the street. But to his wife, Mònica Pàmies Bermúdez, Alzheimer's moved in long ago.





When Mònica feels ready to explode, she seeks refuge in the kitchen. Here at the counter, she can gaze out the window with a cup of tea and stop for breath. Her husband's transformation has been extensive, but it's the small changes she has the hardest time comprehending. For instance, he no longer knows the difference between shaving foam and toothpaste. How is that possible? she asks herself. The man who had so much energy, so many talents?

In the old days, Enric was the chef in their marriage. After work, they'd each hurry home to meet in the kitchen, and he'd do the cooking while she kept him company. His zest for life just bubbled out of him, and every dinner with Enric and her daughter Raquel was a small party. Once in a while the couple still bumps into Enric's old colleagues out in town, and they'll say, "We miss you so much, Enric – you made us laugh!"

The first warning signs arrived so quietly, they barely seemed like signs of anything. Raquel asked Enric not to make anything with potatoes for dinner – and potatoes were precisely what he made. Then one day, there wasn't any dinner at all. "Why should I be your servant?" he demanded to know. "Raquel should do it!" Mother and daughter were bewildered. For 15 years, he'd taken such pleasure in cooking for his family. And he'd always doted on Raquel – why was he suddenly so belligerent?

In 2012, Enric was fired. During the day he lay on the sofa, not looking for a new job, and

Today, several years after Enric was diagnosed, Mònica is a seasoned observer of how Alzheimer's is changing her husband. Enric himself doesn't think that there's anything wrong. "No problem here!" he says, flashing his wife a bright smile.



"Enric had forgotten that Raquel didn't care for potatoes. When he protested against making food, it was because he couldn't find his way around his own kitchen."



during the evening, when Mònica came home from work, they'd get bogged down in arguments that left her more and more confused. One day, in the midst of a confrontation, she said, "Tell me what I just told you." His reaction caught her completely unawares. For he could not reply; he could not remember. She mulled over the signs that her husband wasn't himself, and became convinced: he must be depressed because of the firing. Raquel agreed.

Then one evening, Mònica found herself being mesmerized by a TV programme. And suddenly, all the signs pointed to something else.

Enric had *forgotten* that Raquel didn't care for potatoes. When he protested against making food, it was because he couldn't find his way around his own kitchen. And when she kept losing the thread in a labyrinth of conflict, it was because there wasn't any thread to hold onto.

The TV show was a fundraiser for Alzheimer's.

Big dark glasses

Today, several years after Enric was diagnosed, Mònica is a seasoned observer of how Alzheimer's is changing her husband. Enric himself doesn't think that there's anything wrong. "No problem here!" he says, flashing his wife a bright smile.

Mònica explains that he orients himself by reading people's facial expressions, listening

to the sound of their voices – and then guessing his way forward. The flat is still a safe place for him. Yet outside, dangers lurk. He's begun to regard his illness as a figure that's waiting for him down in the street, that wants to lead him astray. He calls this figure "Mr Alzheimer", and Enric says that he avoids the man's "grip" by not going out alone. As long as Mònica's present, everything's fine. If she doesn't succeed in protecting him against the disease's grip, he bristles. "I'm angry with Mr Alzheimer!" he says then. "Goddamn Mr Alzheimer!"

Enric's sentences flutter with fragments of sense. Yet there's one particular place, Mònica says, where he is able to express himself fully. He goes to an art therapy class once a week, and one of his recent drawings shows serene faces floating like balloons among the trees. From their heads, leafy branches grow, the branches getting entangled with each other and turning into fingers.

But what does Mr Alzheimer look like? Enric grasps a stick of charcoal. His hand knows what it's doing. A face emerges with firm, rapid strokes. It sports a hat with a jaunty feather and large dark glasses. That's what Mr Alzheimer looks like. But why such big glasses? Enric does not hesitate. "Because I wear glasses," he says, quickly removing his pair.

I'm Google Maps

It takes Mònica's full attention just to keep their everyday life functioning. From six in





Enric's sentences flutter with fragments of sense. Yet there's one particular place, Mònica says, where he is able to express himself fully. He goes to an art therapy class once a week.

the morning until about midnight, when she goes to bed, she is attending to the acute needs, large and small, of other people. Before leaving for work, she lays out clothes for Enric and prepares his lunch. At work she juggles clients from around the world, and this job suits her temperament. She relishes the energy and tempo of it – she makes decisions, she cuts to the chase, she jokes with her co-workers without slowing down, and the phone rings constantly. Often it's Enric. For when he's looking for something, he calls her up, and over the phone she helps him find it. "I need to develop a photographic memory to do this," she says, before adding with a little smile, "These days, I'm Google Maps." She always tries to answer patiently and quickly, because if she lets the phone just ring, she begins getting worried. Ten minutes later, he calls again. And again.

And the next day she starts all over from square one.

Raquel no longer lives at home, but she sees how her mother struggles not to buckle under. Recently she offered to drop by every day to make sure Enric eats his lunch. It would take a great weight from her mother's shoulders, because Enric forgets to eat when he's by himself. But Mònica struggled to accept the offer; Enric's *her* responsibility, after all. Raquel insisted. And insisted again. Mònica imitates her daughter's gentle voice: " 'Mama? C'mon, Mama, I *want* to, please let me do it!' " Mònica lets out a shuddering sigh. "Finally I said yes."

She takes a deep breath, then adds, "But I felt so sorry for her."

Transformations

Now and again in the evenings, while Enric's watching TV in the living room, Mònica goes to sit in the kitchen. Out here, the old Enric is closer. She's fond of the walls' deep oxblood colour. She considers the day's minor crises and how, here and now, she can best help her husband. Enric strews his shirts everywhere, and moves their things around. Afterwards he gets frustrated when he can't find anything. And she wonders: is she too strict, for trying to get him to keep the flat in order? Are there better ways to help him?

There are other things that she can't make herself think about. Not yet.

The first time she saw Enric, he was in a group of his colleagues, all looking quite grave. He attracted her gaze with the way he radiated warmth and a passion for life, and she knew: she wanted to accompany that man. "We laughed all the time," she remembers. "We laughed at life."

For Mònica, that moment is a cherished memory.

She has the feeling that he can no longer recognize himself in the mirror. But *she* sees him. She sees with clarity the Enric he once was, and she accompanies the Enric he is becoming.

"The first time she saw Enric, he was in a group of his colleagues, all looking quite grave. He attracted her gaze with the way he radiated warmth and a passion for life, and she knew: she wanted to accompany that man."

ENRIC ÁLVAREZ GUAYTA

Customs broker

Age
63

Residence
Barcelona, Spain

Diagnosis
In 2014, Enric was diagnosed with Alzheimer's disease.

Children
One son from a previous marriage

Employment
Enric worked as a customs broker until 2012, when he lost his job in a round of layoffs.

Everyday life
Enric is no longer capable of making plans or seeing things in a larger context, and he's lost his initiative. Yet he can still stay home by himself. He's always loved drawing and painting, and Mònica makes sure that he attends art therapy and memory classes.



The flat is still a safe place for him. Yet outside, dangers lurk... As long as Mònica's present, everything's fine.

A diary note from Mònica

Wednesday, 30 August 2017

He calls me at work at 5.50, 5.54, 5.55 p.m. I tell him I'm going to the doctor's – not the one in our neighbourhood, but one in the upper part of the city.

At 6.10 he calls me again. "Hi, how are you? What are you doing?" "Well, I'm going to the doctor's, Enric." "Ah okay, okay, I'll see you at home later. I won't go out, I'll wait for you here."

6.15: "Hi, how are you? What are you doing?" "Well, the same as two minutes ago, I'm going to the doctor's."

Three more times in the next fifteen minutes. "Hi, how are you?"

In the end, I tell him: "Enric, don't call me again, I've got a doctor's appointment and I won't be able to pick up the phone while I'm having tests done."

6.45 and 6.52. "Hi, how are you? What are you doing?" Finally I say, "Enric, please get a piece of paper and write DON'T CALL Mònica, SHE'S GOING TO THE DOCTOR'S".

So he does that, though later I see that he's left the paper on my bedside table.

MÒNICA PÀMIES BERMÚDEZ, ENRIC'S WIFE

Freight forwarder

Age
49

Residence
Barcelona, Spain

Children
One daughter, Raquel, from a previous marriage, and one grandchild

Employment
Mònica works as a freight forwarder for an air- and sea-freight company.

Everyday life
Mònica looks after her job and her husband. Some years ago, she took up smoking again, because it calms her down a bit. A local Alzheimer's organization advises her on practical and legal matters.

Mònica's advice for someone whose spouse has recently been diagnosed with Alzheimer's

You need to be very strong. The life you had before will be destroyed.

My husband is maybe 10% aware of his illness, depending on the day. He thinks he is more or less the same person, it's just we who keep misunderstanding him. So the patient suffers from the disease less and less. He's not aware of it. But you are. It's you who will be suffering from Alzheimer's.

If you've said something ten times and that doesn't work, it's your fault and you

have to change your approach. When it gets hard, remember: it's not his fault! It's the illness.

Before this happened to me, I would have said: I could never deal with that. And then you find out you can. But why? Why me? I used to ask that too. But I no longer look for explanations.



The severity disconnect

The perception of Alzheimer's symptoms can vary greatly between patients, their caregivers and their physicians. Recent Lundbeck research reveals that no matter how severe the Alzheimer's diagnosis, the burden of the disease often falls most profoundly on caregivers.

Alzheimer's is a disease that is often characterized by perceived symptoms – reported by the patient, the physician and the caregiver. As the most common symptoms include short-term memory loss, the patient may have trouble understanding or determining the severity of his or her own disease. The caregiver, on the other hand, who usually spends time every day with the patient, experiences the symptoms more vividly and continuously than both the patient and the physician. This is the severity disconnect, and it means the burden of Alzheimer's tends to fall most heavily on the caregiver.

In 2016, Lundbeck engaged in Alzheimer's market research that surveyed more than 600 physicians, 4,600 patient charts, 1,100 patients and 1,300 caregivers across the US and EU.¹ The research found that caregivers often experience the patient's symptoms as more severe than the patients themselves or the treating physicians. It also found that patients often do not understand their condition, so there is a greater reliance on caregivers to manage the disease daily. Caregivers state there is also a greater reliance on them to remind patients to take medication vs. what the patients report themselves.

Why the burden falls on caregivers

Alzheimer's symptoms differ from patient to patient and range in severity, but the most common symptoms include short-term memory loss and finding it hard to concentrate. Symptoms have a high impact on the daily life of 40% of patients, leaving the majority unable to work. Furthermore, between one third and one half of patients are physically inactive and up to one half of patients are socially inactive. This means that many Alzheimer's patients have difficulties being left alone, which places added levels of burden on the caregiver.

Delayed diagnosis affects care

The majority of surveyed patients delayed seeking medical attention when they first experienced symptoms. Physicians, caregivers and patients all agree, however, that the reason was because patients were in denial or afraid of what they might find out. In any case, this could indicate that by the time patients seek care, they are no longer able to manage their own disease. Almost one quarter of patients state they do not understand or feel knowledgeable about their condition, yet they believe there is good communication between their caregiver and their physician.



ALZHEIMER'S DISEASE

15

MOST COMMON ALZHEIMER'S SYMPTOMS

1. I forget things that had only just happened
2. I find it hard to concentrate
3. I forget names and words
4. I have trouble finding things
5. I lose track of time
6. I feel frustrated/agitated
7. I have problems communicating
8. I feel depressed
9. I forget who people are
10. I have problems sleeping
11. I get lost going to or coming from a familiar place
12. I have problems understanding numbers/puzzles
13. I sometime lose motivation
14. I need help with everyday things
15. I feel angry/aggressive

¹ Alzheimer's Disease Atlas, Lundbeck, 2016

² www.alzheimers.net/resources/alzheimers-statistics/

Patients underestimate their reliance

Non-professional caregivers are often a spouse, son, daughter or another family member. More than one third of caregivers do not work. That could mean that for many caregivers, looking after their loved one with Alzheimer's has become a full-time job. They do everything from helping the patient bathe and dress to managing their finances. Nevertheless, physicians report that patients often underestimate how reliant they are on their caregivers.

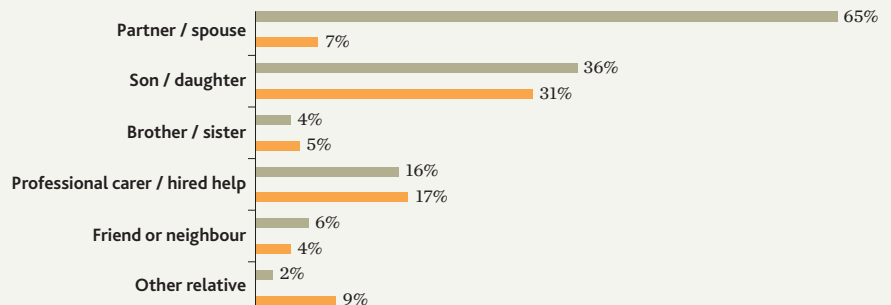
Severity is subjective

The majority of Alzheimer's patients report the severity of their condition to be mild to moderate, while caregivers report the patients to be more severe. At the same time, as the physician has limited contact with the patient, he or she may also underestimate the severity of the patient's symptoms; 39% of physicians underestimate severity vs. caregivers, who are often with the patient every day and responsible for the daily management of the disease.

Alzheimer's is a devastating disease for patients – this much is indisputable. However, when we look at the broader picture and consider the severity disconnect and the disease's impact on caregivers, we can see it creates a demanding and exhausting situation that represents a huge emotional and physical burden. With an estimated 50 million people globally having Alzheimer's or a related form of dementia, the impact on society is substantial.²

Caregivers status

Half of all patients are cared for by a non-professional caregiver; typically the patient's partner/spouse or their son/daughter.



● Patient perspective

Who helps you with your daily needs and activities?

● Caregiver perspective

Other than yourself, who else helps you with the patient's care?

ALZHEIMER'S PATIENT PROFILE

Equally likely to be male or female

Age: early- to mid-70s

Family history of Alzheimer's disease

Not employed

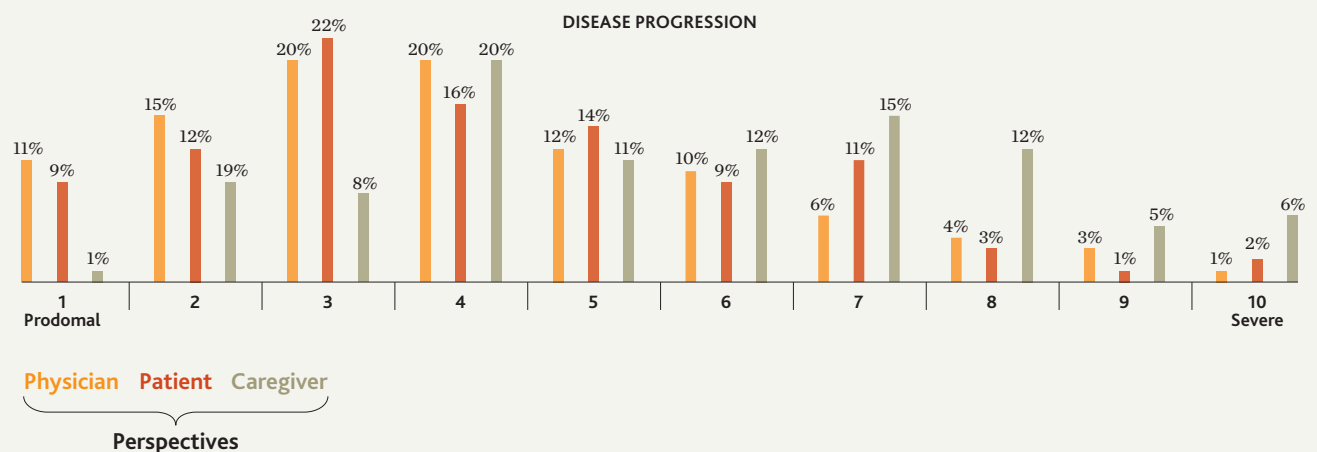
Usually cared for by a younger, predominantly female caregiver

24% of patients overestimate severity vs. physicians

26% of patients underestimate severity vs. caregivers

39% of physicians underestimate severity vs. caregivers

Caregivers report patients to be more severe than reported by either physicians or patients





Taking action to promote sustainability

Since world leaders in 2015 adopted the 2030 Agenda for Sustainable Development, Lundbeck has acknowledged its responsibility in terms of the 17 Sustainable Development Goals (SDG), and six of them in particular.¹

As a global pharmaceutical company highly committed to improving the quality of life of people living with psychiatric and neurological disorders, we take a special interest in Goal 3 and the associated target 3.4: By 2030, reduce by one third premature mortality from non-communicable diseases through prevention and treatment and promote mental health and well-being.

Mental health promotion

In our work to promote mental health and well-being, we share society's concern that suicide is the second leading cause of death among young adults between the ages of 15 and 29, and that depression and schizophrenia too often lead to suicide. We know that mental illness and suicide is something that affects the individual, their friends and families. Many of Lundbeck's affiliates are working to promote mental health and well-being through a number of activities and initiatives. In the coming years, we wish to unite with other stakeholders sharing the same commitment to the SDG on mental health promotion as well as suicide prevention.

DID YOU KNOW?

Mental disorders occur in all regions and cultures. The most common are anxiety and depression, which not infrequently can lead to suicide. In 2015, an estimated 800,000 people world-wide committed suicide, and 86% of them were under the age of 70 with men about twice as likely to commit suicide as women.

Globally, suicide is the second leading cause of death among those between the ages of 15 and 29.

Source: Global Health Estimates 2015: Deaths by cause, age, sex, by country and by region, 2000–2015. Geneva: World Health Organization; 2016.

Cases from our organization

USA

In the US, many initiatives and activities exist regarding mental health in general and suicide prevention in particular. Through participation in corporate advisory councils, Lundbeck in the US helps drive the mental health agenda. We engage with many patient advocacy groups, including those dedicated to addressing suicide such as the American Foundation for Suicide Prevention, in their efforts to raise funds, build awareness, offer education and conduct programs to address mental health issues in the US.

SOUTH KOREA

South Korea has throughout the years been reporting the highest suicide rates in the world. Lundbeck in South Korea is taking an active part in the suicide prevention work at national level and is working closely with the Korea Suicide Prevention Association. More specifically, Lundbeck in South Korea supports a program that provides education and psychological help to families who have lost one of their family members to suicide.

¹ Read more about SDG 3 and the other SDGs on UN's website: <http://www.un.org/sustainabledevelopment>

LUNDBECK'S APPROACH AND SAMPLED ACTIONS

SDGs supported by Lundbeck



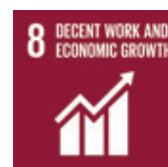
GOOD HEALTH AND WELL-BEING

- We address the global medical unmet need through the development, production and marketing of effective treatments. We engage with patient groups and caregivers to better understand their needs.
- We take responsibility for keeping the patients who need our medicine safe. Our actions are driven by regulatory requirements established by authorities and ethical considerations described in Lundbeck's Code of Conduct.



GENDER EQUALITY

- We offer equal opportunities for men and women across the organization in accordance with our employee policies and guidelines that provide equal opportunities and benefits for all genders.
- Our due diligence procedures for suppliers include their effort to end all forms of discrimination.



DECENT WORK AND ECONOMIC GROWTH

- We ask our suppliers to prevent corruption, provide safe and healthy working conditions, minimize their impact on the environment and respect human and labour rights in the mutually binding agreements we enter into.
- Our OHSAS 18001 certified HSE management system involves our managers and employees in taking prioritized and coordinated decisions that ensure a safe and healthy working environment and the well-being of our employees.



RESPONSIBLE CONSUMPTION AND PRODUCTION

- We minimize the environmental impacts from our research, development, manufacturing and distribution activities via our ISO 14001 certified HSE management system.
- In 2017, Lundbeck recycled 56% of the nine most used solvents and eliminated the need for approximately 1,600 tons of new solvents.



CLIMATE ACTION

- Our long-term CO₂ reduction target is recognized as 'science-based' by the UN, WWF, World Resources Institute and the Carbon Disclosure Project (CDP). This level of CO₂ reduction is required for all nations to keep the global warming below two degrees in 2100.
- We continuously reduce our CO₂ emissions by optimizing our processes and facilities. By the end of 2017, we reduced our CO₂ emissions by 64% compared to 2006.



PEACE, JUSTICE AND STRONG INSTITUTIONS

- Our Code of Conduct represents our commitments to and expectations of our employees for the areas that are critical to the pharmaceutical industry. The Code's anti-corruption principles are supported by corporate and local procedures that include requirements concerning our interactions with suppliers and key stakeholders.
- All employees carry out annual training in our Code of Conduct and we continuously monitor compliance internally and with key partners.



A small caterpillar taking cover under a leaf

The stigmatization of people with depression infiltrates schools and workplaces. It splits families apart. And it's not only the acutely depressed who have to fear rejection; the high-functioning hide their mental health histories too. One of them is 52-year-old Ruth Joseph.



"Ruth has always suffered from sleep disturbances, and when after six months her boy finally slept through the night, she was no longer the same."



Depression entered Ruth's own life back when she was a stay-at-home mother with two small boys. She was living what she describes today as "a dream life" – and yet she felt ashamed. She felt ashamed that she wasn't happy.



Ruth has a demanding corporate job. She is required to drive and deliver on many projects – and keep a cool head while she does it. Her boss and her co-workers know her as an employee they can rely on, and at the same time as someone whose snappy wit makes them laugh. It's the professional Ruth they work and have fun with. A certain side of her remains invisible to them.

The private Ruth is a volunteer counsellor for a text-message helpline for people in crisis. Two nights a week, she listens and texts with a chorus of unhappy voices, many of them quite young. They are depressed, they have anxiety attacks, they cut themselves. And when Ruth encourages them to confide in the people closest to them, she hears a constant refrain in their responses:

*No!
I can't tell my family, they'll be so disappointed in me. My parents will say I'm dramatic, that I'm making this up. I can't tell my school counsellor, he'll tell my parents.*

They tell her that outwardly, they're able to appear happy and positive. Inwardly, though, they're about to collapse in a swirl of painful emotions. "They're all so afraid," Ruth says, and what they fear – or know from experience – is that they'll be judged and rejected as weak and negative. And it's not just young people Ruth engages with. Recently she texted for several hours with a man who wanted to kill himself because his wife had left him and taken their young boys.

Ruth tries to help people who are afraid to talk with the people in their lives. And she

understands. Since her mid-30s, she's slipped into and out of depression, and she knows a great deal about keeping your vulnerability hidden.

Mom is taking a nap

Ruth's family has a strong genetic predisposition to mental illness. Her grandmother, for instance, was committed to a mental hospital for a long period in the '70s, when Ruth was a little girl. Her grandmother's illness was shrouded in silence. The hospital was referred to as "that place", and Ruth knew that she shouldn't ask why Grandma was there. Even today it's something of a mystery.

Depression entered Ruth's own life back when she was a stay-at-home mother with two small boys. She was living what she describes today as "a dream life" – and yet she felt ashamed. She felt ashamed that she wasn't happy. Ruth recalls one particular day when she was walking on the street, and what she calls her "underlying malaise" formed into the thought "I'm so ... nothing. I'm not ... there." She demonstrates with her fingers: *that* small. *That* unreal. During those years, she says, she was a small caterpillar taking cover under a leaf.

Ruth herself believes that what triggered it was long-term exhaustion after the birth of her second son. Night after night, the restless infant would keep her awake. Ruth has always suffered from sleep disturbances, and when after six months her boy finally slept through the night, she was no longer the same. She began to retreat from her surroundings. As often as she could, she drew the blinds to block out the daylight in her bedroom and



slipped under the covers. " 'Mom's taking a nap!' I used to say." Ruth shudders at the memory. "It sounds so weird to me now."

In sleep, she could disappear. Outside the bedroom lurked a world she could not inhabit. She didn't have any strong feelings – other than a hyperirritability that could flare up at the repeated clicking of a ballpoint pen or the sound of someone chewing gum. In childhood, Ruth was taught to suppress her negative emotions, and now she responded to her growing peevishness with an increasingly strict self-control. Yet her anxiety spilled over onto her two boys. Everything they did struck her as dangerous. "Careful!" she kept warning them. "Watch out!"

Outwardly, she was a privileged wife and mother who enjoyed her life. Only her husband and twin sister knew she was in a bad way – and only her sister knew the full story. Ruth did have friends, but no confidantes. Often she was on the point of opening up and then held herself back. But perhaps she wasn't the only one, she muses. When Ruth thinks back on that time of her life, she has no clue how the other women in her circle were *really* doing.

In 2000, Ruth was diagnosed with depression. Yet treatment didn't help much. In 2008,

she got divorced, and today she believes that her depression contributed to the breakup of her marriage.

True happiness

No one at her workplace knows that story, and no one will. It's a friendly work environment, but experience has taught her what can happen to employees with depression. Ruth sums up their fate in a few words: "They didn't fare well." One particular incident at a previous workplace is burned into her memory. A co-worker would occasionally burst into tears; she had mood swings and her performance was uneven. This woman received no help. She was labelled as "awfully unprofessional" and fired. Ruth loves her job and has a lot at stake. "I would never dare to share my history for fear of appearing weak," she says. "The less emotion in the workplace, the better." In her cubicle hang only a few private photos.

But there is one setting where Ruth has broken her silence. A few months ago, she told her parents about how she's struggled with depression for years.

She told them in connection with a difficult conversation about one of her boys. In recent years, Ruth has responded well to treatment,

and she finds herself in stable remission. Yet depression is not absent from her life. Her younger son has had serious psychological problems since he was 12. Now he's in college and lives near campus. Ruth describes him as intelligent, knowledgeable and witty. He's been through many different kinds of therapy and treatment, to no avail. "I hate my life," he tells her.

Ruth's son is stuck in a place in his life where she was once stuck too. He has much to be happy about – but he doesn't feel that way. And like many of the people who text Ruth on the crisis hotline, he blames himself for not being able to pull himself together. He's facing a new type of treatment, and he fears that it too will fail to work. "Won't that mean that I'm lazy and have a bad attitude?" he asked Ruth recently. "Do you want me to pretend I'm happy?"

True happiness and fake happiness can look like each other, but they lie worlds apart. Ruth has known both. She takes pleasure in her life now, and she talks about what a profound difference that is. And she fervently hopes that one day, her son can join her in finding genuine joy.

RUTH JOSEPH

Accountant and a paralegal

Age

52

Residence

Dallas, Texas, USA

Diagnosis

Ruth was diagnosed with major depressive disorder around the year 2000. Her symptom profile includes anxiety. Her family has a marked genetic predisposition to mental illness. Ruth's twin sister and younger son suffer from depression, a cousin has bipolar illness, and her paternal grandmother was committed to a psychiatric hospital for a long period when Ruth was a child. Whatever her grandmother suffered from, it was never spoken of in the family.

Children

Two adult sons in their 20s.

Employment

Ruth is trained as an accountant and a paralegal, but she was a stay-at-home mother until her divorce in 2008. Now she's a mortgage compliance officer at a major bank.

Everyday life

Ruth enjoys running, reading and doing puzzles. Twice a week, she volunteers for a text hotline, counselling people in crisis.



A diary note from Ruth

Wednesday, 1 November – Friday, 3 November 2017



In recent years, Ruth has responded well to treatment, and she finds herself in stable remission. Yet depression is not absent from her life.

My 20-year-old son, who also suffers from depression, is in college and lives near campus. He usually doesn't respond to my text messages, so I asked him to give me a call when he was free.

When he called, I could tell immediately that he was in a particularly negative mood. He's negative most of the time, but that day was worse. When I asked him how he was, what he said made me anxious: how miserable he is, that he's not sure his new depression treatment will work, or that he wants to continue as a college student. After I hung up I felt deflated and hopeless.

Even though I continued to think about him, I kept myself busy with work. Later that evening, I went for a run, watched TV and read – things I do most days. Staying busy is one of the coping strategies I use to manage my moods as best I can.

The next day, when I spoke with him by phone, he seemed better – still negative, but better. I realize that his depression is not in remission, and that he has to learn the best way to manage it himself. I can't change his outlook – much as I would like to.

Cognitive symptoms and the vicious cycle

The negative effects of cognitive symptoms can deepen depression, preventing patients from emerging from their illness and returning to everyday life.

Because of its widespread nature, there is a common wisdom around depression. Globally, over 300 million people are affected by the disease¹ and many people know someone who has struggled with it, such as a friend or family member. The common wisdom includes the notion of 'the vicious cycle' – the idea that the patient struggles to come out of depression because his or her low mood leads to the inability to accomplish tasks, which leads to a low self-esteem, which continues to lower the mood and the cycle keeps spinning.

Overlooked cognitive symptoms

However, this common wisdom around the vicious cycle leaves out one very important component – cognitive symptoms. Cognitive symptoms are often overlooked by both patients and physicians, and include symptoms such as low concentration and attention, forgetfulness and difficulty with words. Cognitive symptoms can lead to a loss of patients' ability to function at home and at work, and this can create problems that contribute to a low mood and low self-esteem, perpetuating the vicious cycle.

Recent market research by Lundbeck took a closer look at how physicians and patients view cognitive symptoms of depression and how the symptoms affect patients' lives.²

The research reveals a relatively low recognition amongst physicians of cognitive symptoms when treating depression, even though they see cognitive symptoms as a risk factor for relapse. These and other such findings suggest that reducing cognitive symptoms could be one important way to help patients living with depression to function better in their daily lives.

Diagnosis vs treatment

One quantitative study, which surveyed 1,096 physicians across nine countries, showed that one third of depression patients present primarily with a cognitive symptom. It also showed that 20-40% of depressed patients are estimated to have cognitive symptoms. Despite this, cognitive symptoms do not feature prominently in the reasons physicians decide to treat depression. The top three reasons to treat are suicidal thoughts, low mood and loss of interest or pleasure. At the same time, two thirds of physicians elect to treat all symptoms generally, without prioritizing cognitive symptoms.

The persistence of negativity

During treatment, physicians report the most frequently mentioned cognitive symptom is 'lack of concentration'. They also report that 'lack of concentration' and the 'inability to



DEPRESSION

"I cannot concentrate. I always got the data wrong. I made various small mistakes at the beginning...until I made a huge one. I felt useless."

Wen, 45, head of planning, CN

"These days I avoid making commitments that will take up a lot of my time, or are out of my control. Because I don't know how I'll be that day, whether I'll have energy."

Alexandre, 34, sales consultant, BR

"Other people had to pick up her [the patient's] slack. It's annoying but it was too much of a hassle to get her to do it. She would say 'yes', but then not do it. It was often quicker just to do it yourself than having to constantly remind her and get all the negative interaction. I felt bad for her, but we all felt it was a relief when she went on sick leave."

Lisa, co-worker, public health institution, CA

"She'll shout at me, 'I lost my key!' And I'll always have to say, 'Calm down! Let's go look for it. First, let's look in your purse.' 99% of the time, the key is in her purse. But her irritability with us is instantaneous, it just explodes because she can't have a logical thought."

Lúcio, Sara's husband, BR

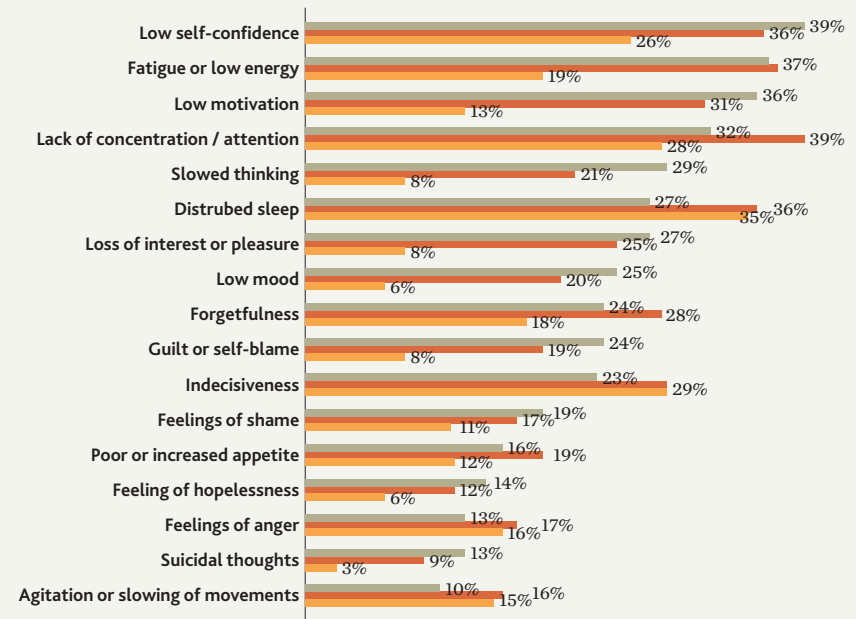
accomplish tasks' have the greatest impact on patients' ability to function at work. And still only one-third of patients are prescribed cognitive behavioral therapy in addition to pharmacological treatment. Half of patients do not receive any cognitive support.

These findings suggest that although physicians consider cognitive symptoms during the diagnosis phase, they do not focus on the treatment of cognitive symptoms compared to other symptoms such as low mood, loss of interest or feelings of hopelessness. This could contribute to persistent feelings of low self-confidence in patients in remission, which feeds the vicious cycle of depression.

The effects of cognitive symptoms on daily life

Despite the low rate of prescribed cognitive behavioral treatment, physicians surveyed in the quantitative study reported that they were aware of cognitive symptoms impacting the patients' home, social and work life.

Physicians feel that 'low self-confidence' most frequently persists in depression patients in remission



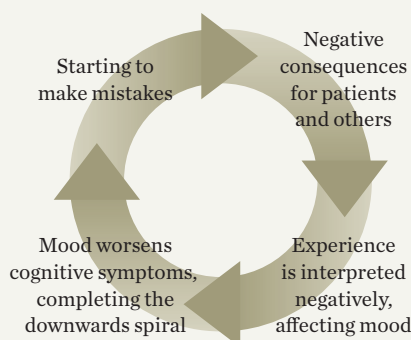
Source: Depression Treatment Landscape study from Nov 2012 - Feb 2013

Base: 1096 interviews with HCPs from 9 primary launch markets (France, Germany, Italy, Spain, UK, Canada, Brazil, China, Japan)

33% average percentage of depression patients presenting primarily with cognitive symptoms – perceived

35% average percentage of patients with depression where cognitive symptoms are a risk factor

The vicious cycle



A different qualitative study by Lundbeck supported this notion, finding that cognitive symptoms have negative consequences that affect mood and perpetuate depression.³

This study found that patients notice their cognitive problems, such as leaving the water running and forgetting their keys in the door, but see them as disconnected from their depression. They saw them more as small, everyday disturbances. But the cognitive symptoms got in the way of patients' ability to start things. They caused patients to make more mistakes and become exhausted by everyday activities. This loss of ability damages patients' work and home lives.

From a personal to social problem

With patients doing less at work and at home, co-workers and family members end up taking on additional tasks. This can be stressful for everyone involved, changing depression from an individual problem to a social one. Co-workers often see the redistribution of work as unequal, creating

tensions and unease in the workplace. At home, patients become dependent, leaving them irritable and ungrateful.

When patients see how their cognitive symptoms affect others at work and home, they feel bad about themselves. This negativity affects their mood, which worsens the cognitive systems, and pulls people deeper into their depression. The vicious cycle escalates the depression, leading to further disengagement from the world.

Common wisdom around depression stops short of cognitive symptoms and how they can affect a patient's life. Although physicians are aware of cognitive symptoms, they are not regularly prescribing treatment to manage the cognitive symptoms, even though reducing cognitive symptoms could potentially lead to fewer mistakes, fewer job losses, fewer divorces and a break in the vicious cycle. Returning to life is the ultimate goal for most depression patients. If they can succeed at this, it benefits not only them, but also their co-workers, family and friends.

¹ World Health Organization, 2017

² Depression Treatment Landscape Study, Lundbeck, 2013

³ Winning Cognition Study, Lundbeck, 2014

Our patient footprint

Since the 1940s, we have been fascinated with neuroscience research, and our development and distribution of pioneering compounds continues to make a difference to patients worldwide. We are recognized for having reached millions of people living with psychiatric and neurological disorders with our inventions. However, there is still a massive need for help. And we are willing to do our part to improve treatments and create better lives for patients.

Our legacy

1940

During the years following World War II, Lundbeck initiated its neuroscience research, laying the foundation stone for the drugs which would later make Lundbeck world famous.



1959

In 1959, Lundbeck launched one of the first antipsychotics in the world, which through the 1960s and 1970s became Lundbeck's most sold product – a new era in antipsychotics for Lundbeck had begun.

1990

Lundbeck expanded rapidly in the 1990s, due to the success of citalopram, which was registered in more than 70 countries for the treatment of depression and anxiety.



1980

At the close of the 1980s, Lundbeck further intensified its business strategy focus. In future, Lundbeck would dedicate its efforts to the research, development, manufacturing and commercialization of pharmaceuticals for the treatment of brain diseases.

1960

In the early 1960s, Lundbeck launched the antidepressant amitriptyline. This marked the start of Lundbeck's interest in antidepressants that would later lead to the discovery of citalopram.





2002

Escitalopram was launched in 2002 and made available in about 100 countries worldwide, growing to account for the major share of Lundbeck's business.

2018

Today, Lundbeck is a global pharmaceutical company focused on developing innovative treatments for depression, schizophrenia, Parkinson's disease and Alzheimer's disease.



Our commitment

At Lundbeck, we are committed to continuing to improve the lives of people living with psychiatric and neurological disorders.



DEPRESSION

300 mio.¹



ALZHEIMER'S DISEASE

50 mio.¹



SCHIZOPHRENIA

21 mio.¹



PARKINSON'S DISEASE

6 mio.²



million is the estimated number of patients treated with Lundbeck's legacy portfolio of invented products in 2016³



¹ WHO, 2017

² The Lancet, Global Burden of Disease Study, 2017

³ Lundbeck calculations based on IMS data and insights from Decision Resources Group





Try to treat Parkinson's like an old friend

As an 80-year-old with Parkinson's, how do you coax the best quality of life from your daily existence? A lifetime of experience and zest for life is showing Sheng Kanghua how.

SHENG KANGHUA

Engineer

Age

80

Residence

Beijing, China

Diagnosis

Diagnosed with Parkinson's disease in 2008, Sheng Kanghua's symptoms include tremors, muscle stiffness, memory impairment, poor sleep, dizziness and dystonia, which in his case involves sudden, intense stabbing pains in the hands and feet. He exercises several times a week, which has helped to alleviate his symptoms, including the muscle stiffness, and delay progression of the disease. And a scan has shown that exercise has kept his bones as strong as a much younger man's.

Marital status

Married to Mrs Feng

Children

One daughter and one son

Employment

Sheng Kanghua is an engineer. After completing his education, he was employed by a state-owned company, where he worked in public building design. In 1998, he founded a private firm that did interior design for hotels and public offices. He ran the business until he retired.

At present, Sheng Kanghua keeps busy with travel, politics and photography. He particularly enjoys photographing buildings and cityscapes. He gets together with his friends often, and recently, he and his wife have been spending time together in the kitchen, investigating new dishes.





Sheng Kanghua was 71 when he received his diagnosis, and he'd never had any serious health issues before. A faint trembling in his right hand was the only visible sign that the connection between his brain and his body was deteriorating.

It is now nine years since Sheng Kanghua sat in a waiting room, hoping that the doctor would dismiss his forebodings.

When he left the doctor's office, his thoughts kept returning to Deng Xiaoping, who for years was the most powerful politician in China. If Deng Xiaoping couldn't be cured of Parkinson's, there was no hope for him either.

Sheng Kanghua was 71 when he received his diagnosis, and he'd never had any serious health issues before. A faint trembling in his right hand was the only visible sign that the connection between his brain and his body was deteriorating.

In the months that followed, he came close to despair. He envisioned a wasted figure in a wheelchair – that would be him at some point in the future, he was sure of it. Since boyhood, he had been part of a group of old schoolmates who had stuck together. All of them were in good health, but some of them had parents with severe Parkinson's. These parents couldn't feed themselves or get out of bed, and they were racked with pain. Their sufferings seemed to confirm his worst fears.

"Can't be cured", Sheng Kanghua thought, "Can't be cured."

"Everything will be different if you treat Parkinson's like an old friend, rather than an enemy."



Like a friend

During the course of a long life, Sheng Kanghua had to confront many hardships, and he discovered he was a man who strove to get more out of life than just what lay in front of him. At 51 – an age when many of his colleagues had begun to look forward to retirement – he quit his steady job and, flying in the face of all warnings, started his own business.

In the difficult time after his diagnosis, that willingness to buck the odds was reawakened.

Today, nine years later, through a systematic effort that involves exercising regularly and following his doctor's instructions, he has succeeded in delaying the progression of his disease. Not in stopping it, for that isn't possible – but in delaying it. He has more symptoms now than in the first years of the illness; it's become hard to get a good night's sleep, or even to turn over in bed. Painful spasms shoot through his hands and feet. And he cannot recall all the Chinese characters he once mastered.

Yet he feels better than when he was less sick. Life is better. The difference, he believes, lies in his mental attitude, an attitude he sums up in a piece of advice to other people living with the disease:

"Parkinson's will be with you for the rest of your life. So it's important to think about how you want to deal with it. If you see it as your



It doesn't pain Sheng Kanghua to accept assistance from his family either. On the contrary. After a long life of being self-reliant, he has discovered that being open to help is enriching his old age.

enemy, you will allow hatred into your mind and hurt yourself. Instead, try to treat Parkinson's as you would a friend. You need to observe it, communicate with it, understand it. Ask yourself: What does the illness need?

Everything will be different if you treat Parkinson's like an old friend, rather than an enemy."

Balancing act

One of Sheng Kanghua's great joys is to travel. He relates how, after his diagnosis, he accepted the offer of a wheelchair when he got off a plane. And he enjoyed using the service. He walks crookedly and more slowly than people who are well, and it was very pleasant not having to navigate the airport crowds. Yet the next time he flew, he insisted on walking from the plane himself. "I mustn't grow dependent on others," he says, "and lose the ability to do things on my own."

Sheng Kanghua quotes a well-known Chinese proverb to express the daily challenge he faces in living with Parkinson's. He has to find a balance between insisting on his independence and accepting assistance when he needs it. *Ná de qǐ, fàng de xià*, it goes – literally, "Pick it up or put it down." Sheng Kanghua explains the proverb this way: "It means that sometimes, I should hold on very tightly and enjoy doing what I'm still able to do. Other times, I need to accept the inevitable and let go. And I should know when to do what."

As a result, he doesn't refuse necessary assistance. But that requires another balancing act – between himself and his surroundings. "I want to maintain a strong image in front of others," he says. So if anyone other than his close family and friends sees him struggling, he prefers they take no notice.

With good friends it's different. He still meets his old schoolmates regularly in the club where they hang out. As they chat and eat lunch at the round table, his best friend unobtrusively places food on his plate.

It doesn't pain him to accept assistance from his family either. On the contrary. After a long life of being self-reliant, Sheng Kanghua has discovered that being open to help is enriching his old age. He's no longer capable of bending over and bathing his feet. Now his family helps him do it, and he finds their kindness reassuring and touching.

Ná de qǐ – fàng de xià.





PARKINSON'S DISEASE

Parkinson's is the second most common age-related neurodegenerative disorder after Alzheimer's disease. An estimated six million¹ people worldwide have Parkinson's. Classic symptoms of the disease include muscle rigidity, tremor, slowness of movement and balance problems. These are known as motor symptoms. Non-motor symptoms are also common and include depression, dementia, pain, insomnia and dysfunction in the body's autonomic systems (digestion, blood pressure, etc.). Both types of symptoms make Parkinson's difficult to live with, especially as the disease progresses and the severity of symptoms increases.

Lundbeck recently engaged in market research to try to understand how these symptoms are treated by physicians and what their biggest challenges are in terms of controlling the disease. Over 4,000 patient records and more than 700 physicians (neurologists, movement disorder specialists and primary care providers) were surveyed across six countries.² In the survey, physicians ranked the key 'unmet needs' according to segments classified by the patients' stage of the disease. The top three unmet needs across all segments were 'slowing down the course of the disease', 'disease modification' and 'maintaining quality of life'.

¹ The Lancet, Global Burden of Disease Study, 2017.

² Parkinson's Disease Specific Programme, Lundbeck, 2016

The 'off-time' treatment challenge

While physicians are increasingly effective in treating motor symptoms of Parkinson's, the challenge remains of controlling the period when the positive effects of treatment have worn off.

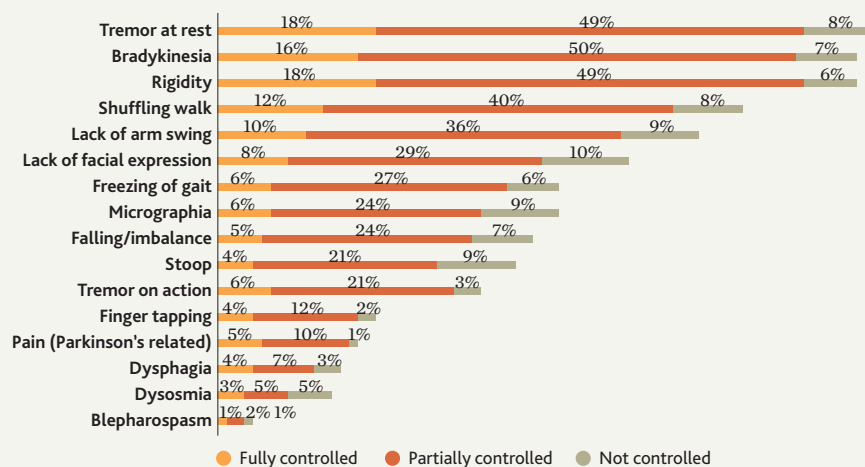
Controlling immediate symptoms

The unmet needs of Parkinson's are relatively long-term challenges, which highlight the fact that while treatments are available for the immediate symptoms of the disease, there are few long-term solutions. There is no cure for Parkinson's. The aim of treatment, generally, is to control and relieve symptoms so that people can enjoy a reasonable quality of life for as long as possible. This approach is corroborated by the survey, where physicians reported they are mainly looking to treat the

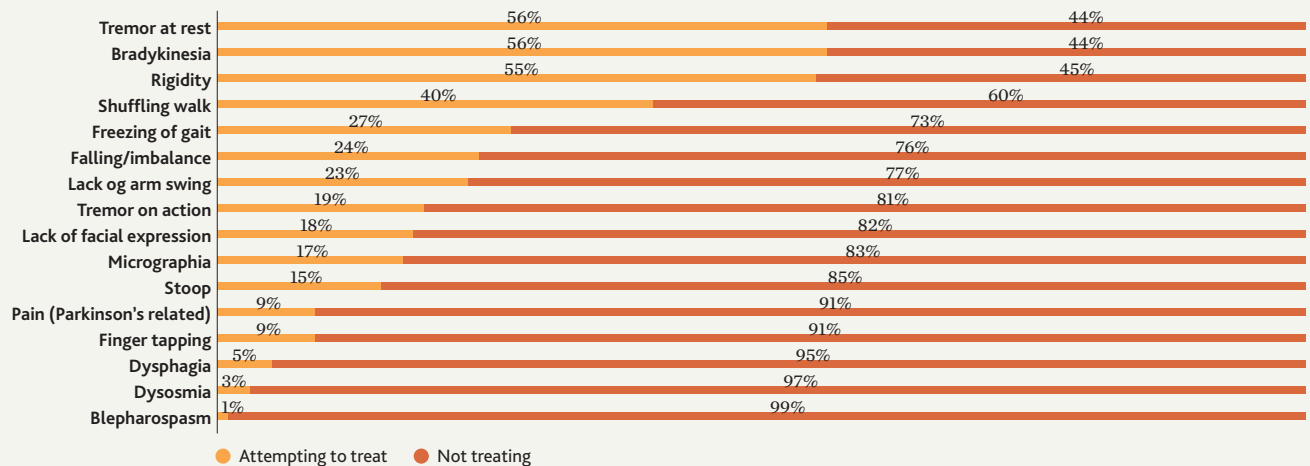
cardinal motor symptoms, the severity of which increase with each stage of the disease.

Despite specifically treating patients for motor symptoms, physicians reported that only a small number of patients' motor symptoms are being fully controlled. This suggests that symptom management may be a more immediate unmet need, and may explain why physicians say that they have a challenge in controlling off-time.

Controlling patients' motor symptoms



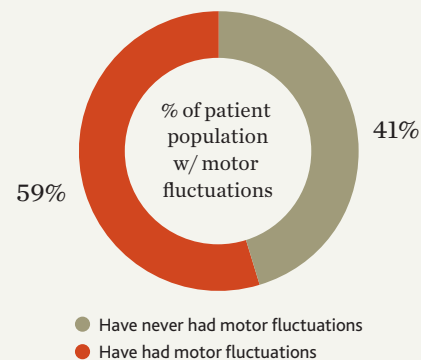
Motor symptoms physicians are trying to treat



The 'wearing-off' effects of medication

According to the Mayo Clinic, patients often experience an improvement in symptoms once beginning treatment. Over time, however, the benefits of drugs frequently diminish or become less consistent. This causes the wearing-off effect – a fluctuation in the symptoms a patient is suffering depending on the effects of the medication. The Lundbeck study reveals that three out of five Parkinson's patients have experienced motor fluctuations, possibly due to the wearing-off effect.

Cases involving motor fluctuations

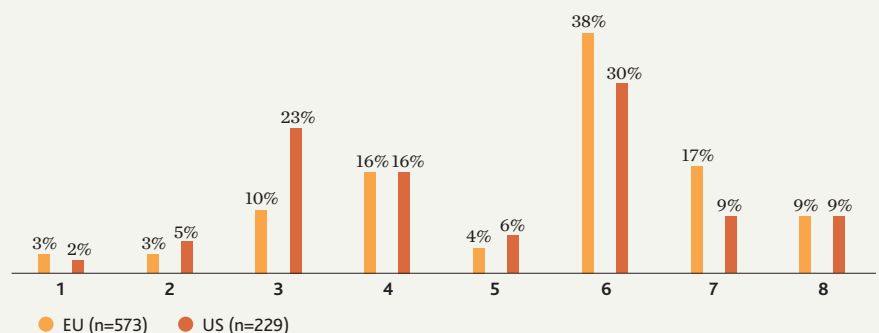


Off-time is the term used for the period when symptoms return after the positive effects of medication have worn off. One prevalent symptom of Parkinson's is known as dyskinesia, an abnormal, uncontrolled, involuntary movement that can look like fidgeting, writhing or wriggling. It doesn't happen to everyone and it occurs at varying degrees of severity. But the study showed that dyskinesia is more prevalent during wearing-off periods, which underscores the physicians' challenge with off-time.

What's the solution to off-time?

The key takeaways from the physician survey indicate that an intervention or medication that is applied late in the disease could combat off-time and improve motor symptoms for patients suffering symptom fluctuations. Such an intervention could delay the requirement for deep brain stimulation or other surgical interventions commonly applied late in the disease. As surgical treatments can be risky, many patients consider non-surgical alternatives to be more acceptable. As patients age and the severity of their symptoms increase, key challenges for the entire Parkinson's community are managing both motor and non-motor symptoms and increasing quality of life. With a non-surgical treatment option for late-disease symptoms, these challenges could be more easily met. This could be a positive development in treatment of the disease, as researchers continue their quest for a cure.

Prevalence of dyskinesia by patient segment



- Initial drug treatment for PD/satisfactory response
- Sub-optimal response to initial treatment
- Maintenance phase ('honeymoon period') No significant dose fluctuations or dyskinesias or cognitive problems

- Sub-optimal response during maintenance phase
- End of dose deterioration: early or severe wearing-off without dyskinesia
- End of dose deterioration: early or severe wearing-off with dyskinesia

- 'On-off' phenomenon
- Palliative phase: therapies exhausted, optimal medical treatment failed



Cognitive and knowledge-based analytics

At Lundbeck, we are always looking for ways to accelerate the development of innovative medicines to treat psychiatric and neurological disorders. Thus in 2017, we entered into partnership with IBM Watson Health in order to combine our neuroscience expertise with IBM's cognitive and knowledge-based analytics. The collaboration will help us establish an innovative approach and new platform for real world evidence and advanced analytics where we can take advantage of Watson technology across clinical data from millions of anonymized patient lives made available through the Watson Health Cloud. IBM can help create data-driven hypotheses based on Lundbeck's questions, which can then be used in further research on fighting psychiatric and neurological disorders.

Lundbeck and the fascinating brain

Essential to Lundbeck's efforts within psychiatric and neurological disorders is to maintain strong internal research and development capabilities in order to establish optimal networks and partnerships. We continue to build external alliances to supplement our internal capabilities, taking advantage of the increased opportunities provided by innovative technologies.

Nurse shark antibodies

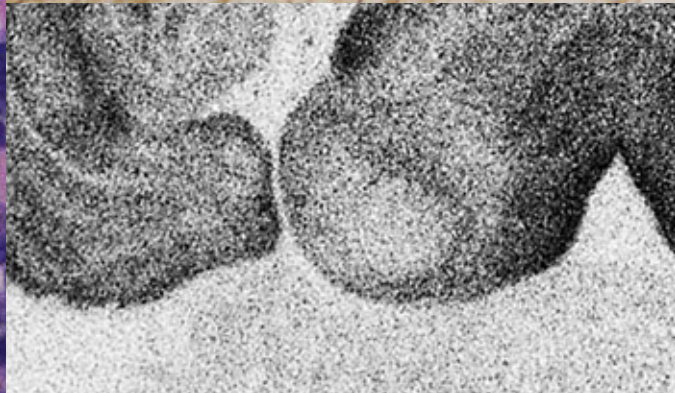
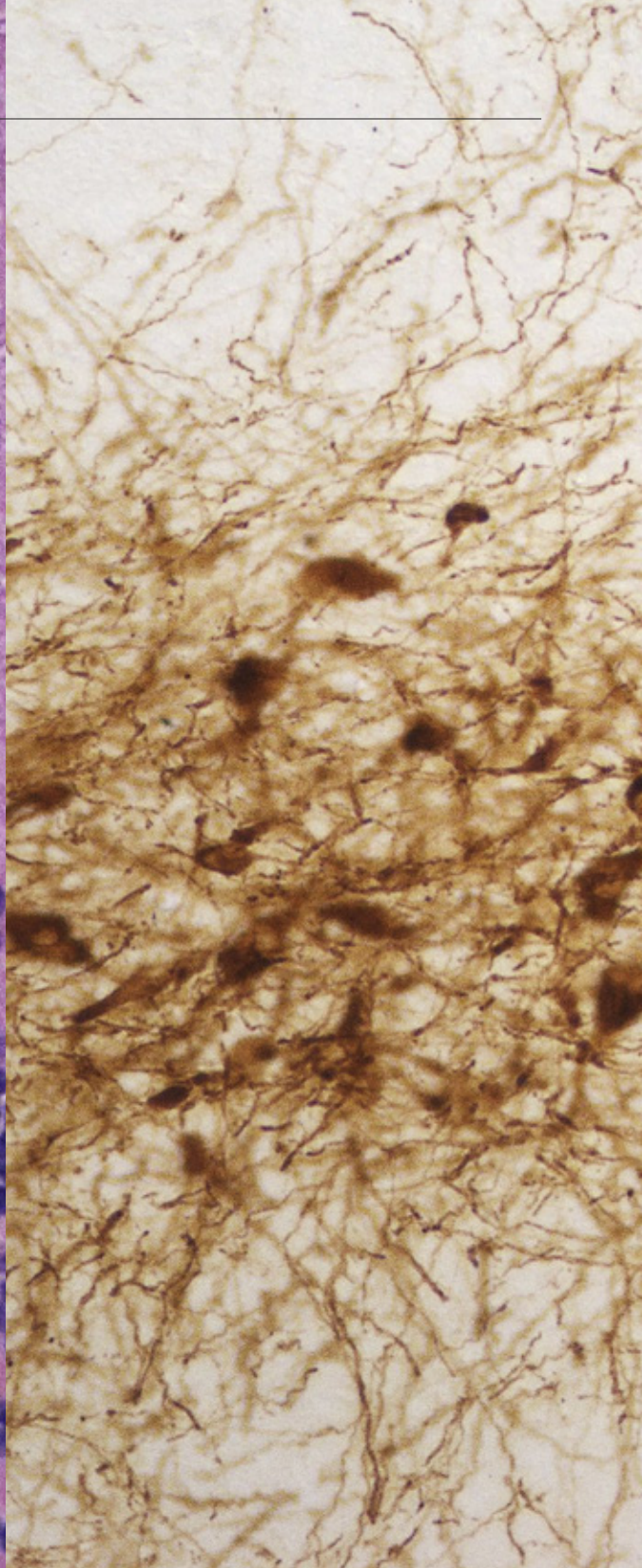
Leveraging 400 million years of evolution, Lundbeck and biotech company Ossianix reached a scientific breakthrough in 2017 in the work to use shark antibodies to enable delivery of therapeutic drugs into the brain. Combining our expertise in the human brain and its diseases with Ossianix's tools to utilize shark antibodies for use in humans, we can create a new technology based on an antibody from a nurse shark that can be used to transport human antibodies treating Parkinson's disease and Alzheimer's disease into the brain. In practice, the method is to attach the human antibodies to the shark-derived antibody, which acts as a transporter across the blood-brain barrier protecting the human brain. This new technology may pave the way for many new and better treatments of psychiatric and neurological disorders, even some that can't be treated today due to the blood-brain barrier keeping therapeutic drugs from entering the brain.

Personal genetics and DNA-testing

Building on Lundbeck's continued work to enhance the understanding of the underlying disease biology and its links to clinical characteristics, we have in 2017 initiated a new and groundbreaking research project with personal genetics company 23andMe, Inc. and think tank the Milken Institute. As a result, 25,000 patients have been enrolled in a large study to explore the underlying causes of depression and bipolar depression and how these disorders and brain functions such as attention and decision-making are related to genetics. The patients' DNA is tested and they must complete cognitive tests and surveys. It is the first time these elements have been combined to study disorders such as depression and bipolar depression. The study addresses two main challenges in treating these disorders: the fact that patients can be very different both with regards to symptoms and to the biological processes leading to these symptoms, and that patients may respond very differently to treatment.

Gene-modified mice

In 2017, researchers at Lundbeck made breakthrough discoveries giving hope for new treatments of schizophrenia. We have identified several mechanisms in the brain which are not targeted by current treatments, but show that they are part of the underlying disease biology. Using gene-modified mice, also invented by Lundbeck, we have been able to conduct research in organisms with the same DNA-mutations found in schizophrenia patients. Further, we utilized highly advanced machine learning techniques to analyze the separations between healthy and ill brains, and how to normalize the function of brain cells that were disrupted because of exactly these DNA-mutations. Schizophrenia symptoms are believed to be caused by miscommunication between brain areas. The miscommunication may be caused by lack of synchronization of the activity of neurons in the brain. Normalizing synchronization of neurons is expected to improve communication between brain areas and thereby treat the symptoms of schizophrenia. We have tested this approach in different DNA-mutations leading to schizophrenia, and the identified treatments were able to normalize brain cell function in all of them.





A

ntibody fragments from llamas

Adding to our early research efforts at Lundbeck, we announced in 2017 a new cooperation with Belgian biotech company Confo Therapeutics, providing us with access to their very special technology platform. This platform is based on the development of antibody fragments from llamas and other camel animals, so-called Confobodies. The goal of the collaboration is for us to deploy the Confo technology to discover novel, small molecule therapeutic compounds acting upon two G-protein coupled receptors (GPCRs), and as a result create new options and concrete medical candidates within the treatment of disorders like depression and schizophrenia. The antibodies of llamas are special because they are much smaller than other antibodies, making it possible for us to hit biological targets that it is not possible to reach with bigger antibodies. Ultimately, this technology will lead to the discovery of a whole new type of potential compound which we have not been able to develop previously.

J

oining forces in the fight against Alzheimer's disease

At Lundbeck, we realize that if we want to do our part in the fight against the feared and complex Alzheimer's disease, we have to join forces with other players in the pharmaceutical industry. It requires a global effort.

Not since the year 2000 has a new drug against Alzheimer's disease been approved and brought to the market – we simply do not know enough about why the disease hits, which makes it very difficult to develop a treatment against the disease or even against the progression of it. In the hopes of continuously learning more about the disease and the underlying disease biology and one day finding a cure against it, Lundbeck is committed to investing in neuroscience research as well as interdisciplinary partnerships and projects.

In 2017, Lundbeck entered into several exciting collaborations. New joint partnerships include peers and competitors within the pharmaceutical industry as well as a number of universities globally. We hosted a research conference in Boston, USA, in search of inspiration and new partnerships with the innovative biotech industry and pharmaceutical research environment. We have furthermore initiated several publicly funded research projects alongside other medical companies, both in Europe and the US.



The eyes follow her, unblinking

For a fearful child, a vivid fantasy world can be a refuge. It was for Ditte Grauen Larsen, who's now 26. But it also opened a door to a universe where eyes on the leaves of trees were watching her, and where reality was as slippery as a skating rink.



Someone who mumbles to themselves on the bus – drunk, perhaps? Perhaps crazy? Anyone can spot a person like that from far away, says Ditte, and would quickly avert their gaze and sit somewhere else. Back in her schooldays, Ditte often felt that her classmates saw her that way. The odd girl. Today she still wonders why that happened. When she looks at her school photos, she sees an unassuming girl with long hair who doesn't stand out at all.

The girl in the school pictures is smiling. It's a façade. Her mother was diagnosed with a life-threatening brain tumour when Ditte was quite small, and the fear that her mother would die put her in a permanent state of alert. About the same time that her mother became ill, her parents divorced, and throughout her childhood, Ditte did her utmost not to be a bother. She was so agreeable that she was barely there, and once in a while she would disappear entirely. She disappeared into a magical world of fairy tale and fantasy, a world in which a family of gnomes might well be living under a stump in the forest. In that world, she herself was a pixie. And if some grownup frightened her with an outburst of anger, it was because the man was in fact a troll.

From 7th through 10th grade, Ditte had to endure a special form of agony – and like so much else, it was something she submitted to quietly. It might appear harmless: every morning she rode the bus to school, every afternoon, back home. But twice a day, the bus ride would hammer home the extent of her isolation. Ditte now thinks that her inner self fractured – right there on the school bus – sometime during 8th grade, long before she became mentally ill.

Today, as an adult, she can see the 14-year-old Ditte before her on the bus. The cool kids





are sitting in back, the losers in front. Teenage Ditte has seated herself in the first row of the back half, in the hope that she'll be teased less than up front. The bus is jam-packed with rowdy students, shrieking with laughter. Are they making fun of her? She's sure that they are. The seat next to her is empty.

And grown-up Ditte says, "No fantasy can save that girl."

A better girl

Time and again while she was growing up, Ditte tried to reinvent herself as "a new and better girl", one who would fit in. She was tirelessly optimistic and pleasant. She wore the same clothes as the popular girls. She smiled and smiled, while behind this front, her inner world grew in strength. In many ways, it became far richer and more fun than her everyday life. If she grew bored during a class, she could self-hallucinate and make a teacher's hair shift colour from white to purple. Or she could conjure up a small lion and watch it act out a scene from *The Lion King* on the teacher's desk.

But then her inner world began to leak into the outer world, and it did so in ways she couldn't control. A host of obsessive thoughts began to haunt her: One of her teachers was a witch, and if the witch's initials were on the bus's number plate, Ditte couldn't allow herself to get on. And she could only wear socks that weren't the same, never ones that matched.

The storm in Ditte's mind raged and gathered strength. Songs she'd heard in the course of the day piled up and played simultaneously. Thoughts whirled around with no object or focus. "All sense of direction vanished," she explains. "I couldn't concentrate on just one thought, for there were a thousand others that were equally urgent."

And simple actions could be lethal. To ride the witch's bus would kill her mother. To put on tights with matching feet would kill her mother. The responsibility for keeping her mother alive rested on Ditte's shoulders.

During high school, Ditte started taking antidepressants. But the medicine didn't change anything about her reality or her struggle to keep it hidden. "My façade meant everything to me," she says today. "I used all my energy to maintain it."

A turning point

The eyes did not blink, and they followed her, depending on where she was. Ditte had the sense that they wanted to make sure that she executed her compulsive actions correctly.

The eyes were real. They were just as real as trees and as the leaves on trees, and it was from the leaves of the trees that the eyes were watching her. Ditte didn't talk about the eyes, for perhaps it was perfectly normal to see them. Perhaps other people saw them too, and would judge her as weak because she was afraid of them. Or they would judge her as crazy, and in that case she would surely be committed and never let out again. Either way, she thought, to speak was more dangerous than keeping quiet.

Ditte had travelled a great distance before she got to the place where the leaf-eyes monitored her. Something in her core had cracked when she was around 14, and later, the cracks had deepened. They manifested as social anxiety, as depression, as obsessive thoughts and self-harm – until finally they erupted in psychosis. That was late 2012. She was 20 years old, and since graduation she'd been working in a supermarket. Several months before, she'd sought out a psychologist, who'd advised her to stop taking her antidepressants. She should quit cold turkey, he'd said.

Then the leaf-eyes appeared.

Ditte had made her mother promise never to hospitalize her. But there was one intervention that Ditte would agree to. The local mental health centre had an outpatient programme for early detection of psychosis, and mother and daughter contacted them.

The first consultation there became a turning point for Ditte. She was immediately directed into treatment. Yet the diagnosis itself distressed her mother greatly. Ditte felt the opposite – that a burden had been lifted from her shoulders. It was not normal to suffer as she had; healthy people didn't feel the way she did. She couldn't be expected to endure it.

A child's mask

Today, five years after that winter, Ditte works as a schoolteacher. She's found places to anchor to within herself – and she's become someone whom others rely upon. She now believes that her years of silence created a cage around her, and that being open about her diagnosis can set her free.

But openness doesn't spare her from being hurt, and her vulnerable spots are frequently under threat. When she became homeroom teacher for an 8th-grade class, one of the mothers googled Ditte and discovered that she'd given talks on her schizophrenia. The mother wrote to the parents of the other students, saying that the new teacher made her extremely anxious. "I got frightened," Ditte recalls. "Would the parents all reject

me? Would I lose my job?" Her first impulse was to keep it to herself. But after confiding in a colleague, she told the school principal. And the principal told Ditte not to give it another thought; she had Ditte's back.

Ditte recognizes that, with her background, she is not like other people. But her troubled past has also given her special skills. She has an instinct for others' moods. She can detect tiny shifts in facial expression, and she has a heightened sensitivity to children who are not thriving psychologically. Ditte can sense when it isn't the child but the child's mask that is smiling. Such children don't always know what they might have to tell. Yet Ditte knows how to ask.

A door opens

A small girl, looking at her hands during naptime. She's pretending that each of her fingers is a person. That's Ditte's earliest memory. And now she herself has become a person who studied to become a teacher, even though the therapists cautioned her not to, predicting that she would fail. She became a person who is performing well in a demanding fulltime job. She became a person who took in an abandoned kitten with a raging eye infection, a kitten that's grown to be a sturdy tomcat and part of her little family. And now another door in her life is about to open.

Ditte's going to have a baby with her boyfriend. She's always wanted to be a mother and knows just the sort of mother she'll be – hardly a model housewife, she says: "I'll be the mom who builds forts of blankets and pillows and chairs. I'll be the one who dresses up to go trick-or-treating with her child." Ditte's face is wide open and full of joy as she describes what she sees in her mind's eye. This is Ditte's own face, and she's not afraid to show it.

Ditte recognizes that, with her background, she is not like other people. But her troubled past has also given her special skills. She has an instinct for others' moods.



DITTE GRAUEN LARSEN

Schoolteacher

Age

26

Diagnosis

Ditte was diagnosed with paranoid schizophrenia in 2012. She has not taken any medications to treat mental illness for a couple of years now, and she is no longer being followed by the mental health system. In connection with her pregnancy, she is being seen by a visiting nurse to make sure that she feels comfortable and psychologically stable.

Residence

Lejre, Denmark

Marital status

Living with her boyfriend, Hans Henrik

Children

Ditte is expecting her first child

Employment

Primary schoolteacher

Everyday life

In her free time, Ditte gives talks on schizophrenia for staff at community mental health centres, continuation schools and nursing schools. She hopes to make such talks a larger part of her professional working life. The woods nearby remain a refuge. She describes them as being a safe haven with a spirit of something ancient and marvellous, a place where she feels protected.

Contrary to doctors' expectations, Ditte's mother was able to survive with her tumour, and she is still alive today.



Ditte's appeal to people who are in close contact with children, either privately or professionally

During my childhood, I strove to be a model daughter. I didn't want to be the slightest trouble to anyone.

Teachers considered me "a good girl", and they seated me next to the kids who were struggling. I was supposed to be a sort of scaffolding for them. I was supposed to be responsible for them *too*. Yet I did give small hints that I was unwell.

It isn't always the child in obvious psychological distress who has the toughest time. Will you try to be attentive to the subtle signals that some kids may be sending, and consider whether they might need help?

A diary note from Ditte's life

Monday, 25 September 2017, 6 a.m.

Woke very early this morning, drenched in sweat.

I dreamed that a psychic was reminding me that I'd never live to see 30. In itself a ridiculous nightmare, perhaps, yet when I woke up I was almost in a state of panic. It brought back a feeling that I'd forgotten – the fear of death.

For a time when I was ill, I was convinced that I'd never grow old. Initially I was sure that I'd never reach 20 – and then when I turned 20, my death sentence was postponed until I become 30.

When I suddenly dream something that reminds me of what can go on in my head, I get an ambivalent feeling, of both fear and pride. Fear that it's a sign I'm about to become ill again; is it normal to think such thoughts? And pride that today I am well, for getting there has been the hardest struggle of my life!



SCHIZOPHRENIA

T

he World Health Organization estimates that schizophrenia affects more than 21 million people worldwide. The disease is characterized by episodes of psychosis (losing touch with reality) in between periods of blunted emotions and withdrawal. There are two categories of symptoms associated with schizophrenia: 'positive symptoms', which occur during episodes of psychosis and can include delusions or hallucinations; and 'negative symptoms', which occur during episodes of withdrawal and can include reduced emotions and reduced feelings of pleasure or interest.

In an effort to understand current prescribing patterns of anti-psychotic treatments, Lundbeck has carried out a global market research survey of 950 physicians and 5,450 patient records across 13 markets.¹ The physicians reported three primary challenges of prescribing anti-psychotic treatments: control of metabolic side effects (including weight gain); control of negative symptoms; and adherence to anti-psychotic treatment. In fact, about half of physicians surveyed reported adherence as an unmet need.

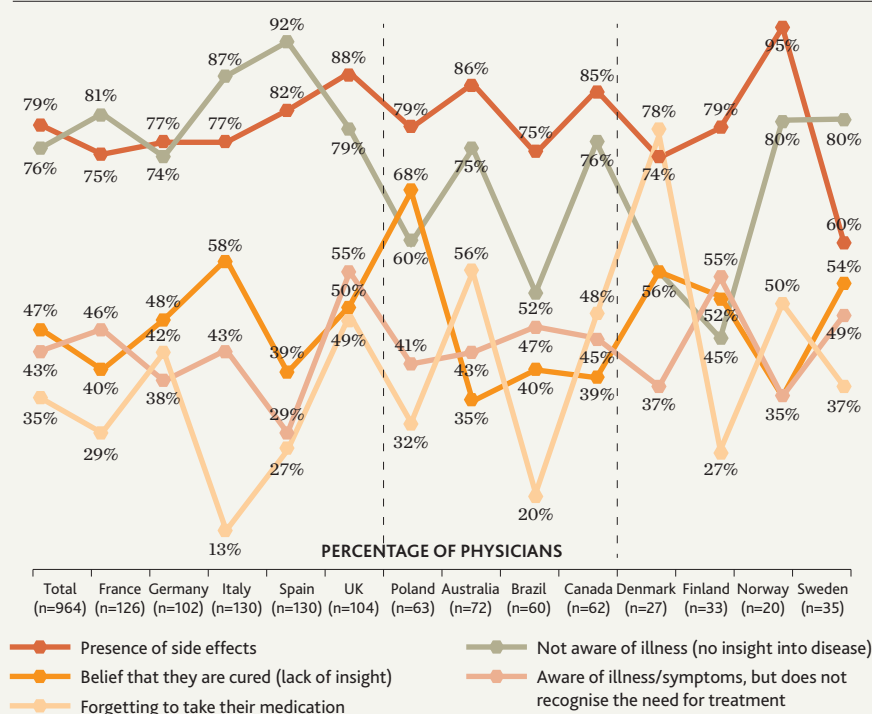
The adherence picture

Physicians estimate that just under half (46%) of their schizophrenia patients are fully adherent to their anti-psychotic medication; 35% are partially adherent; and 19% are non-adherent and take their medication only occasionally or not at all. Patients who are less adherent are more likely to be living alone than patients who are fully or partially adherent.

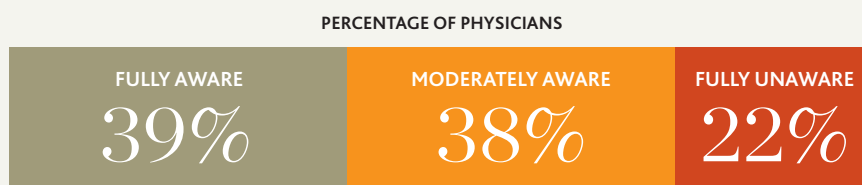
Adherence – a determining treatment factor

Less than half of schizophrenia patients fully adhere to their anti-psychotic medication regimen. This has implications for how physicians decide to treat.

What are the main reasons for patients' non-adherence to anti-psychotic treatment?



What proportion of patients fit into each of these categories in relation to awareness of their schizophrenia?



The main reasons for non-adherence, the physicians believe, are side effects and anosognosia, which is lack of patient awareness of the disease. Anosognosia can take several forms. It could mean that the patient doesn't believe they have the disease. It could also mean that the patient believes they are now cured of it or that they don't recognize their need for anti-psychotic treatment. In any case, the survey suggests that 62% of patients are only moderately aware or fully unaware of their disease.

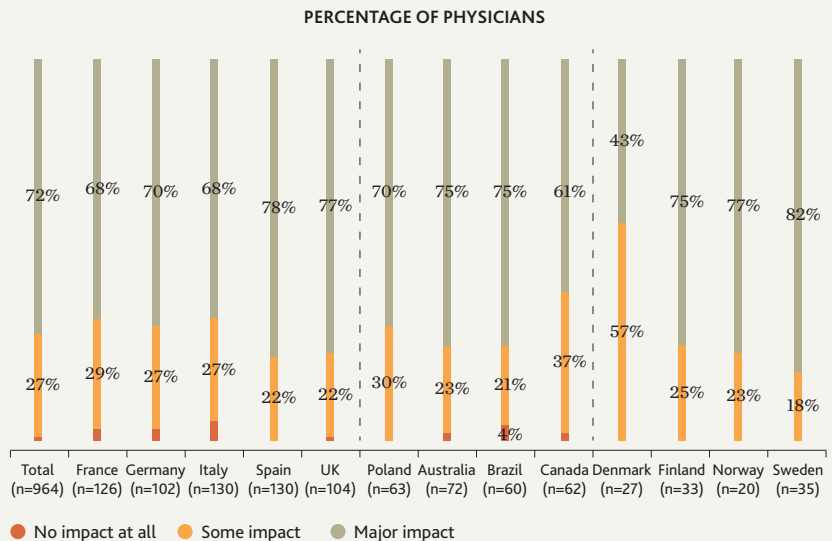
The consequences of anosognosia

Anosognosia can affect schizophrenia patients in profound ways, including worsening symptoms of the disease, lowering general functioning and lowering quality of life.

However, the main consequence of anosognosia reported by physicians is non-adherence to anti-psychotic treatment, which, of course, further undermines the disease. This presents a challenge to physicians when deciding on a treatment course for patients.

Does the presence of anosognosia and the likelihood of adherence factor into the physician's choice of treatment? The answer is 'yes' – when physicians are asked specifically. They report that they are more likely to prescribe an LAI (long-acting injectable) to a patient with low awareness than high awareness. However, when physicians are asked in a broader context, the patient's level of disease awareness is a comparatively minor consideration.

How much impact does the patient's level of awareness of their schizophrenia have on anti-psychotic treatment choice?



Why LAIs for patients with low awareness?

There are several reasons why physicians might be more likely to prescribe an LAI to patients with low awareness of their schizophrenia. Because they are administered by a healthcare professional, LAIs provide a mechanism for monitoring adherence with injections. If non-adherence becomes an issue, this can be identified early. Also, with LAIs, patients are not solely responsible for taking their medication and it does not have

to be taken daily – two factors that increase the likelihood of adherence. According to patient profiles in the survey, patients on LAIs are more likely to be fully adherent and have lower levels of awareness compared to patients receiving medication orally.

Adherence to anti-psychotic medication is a big challenge for many schizophrenia patients. So is anosognosia, which affects over half of patients and leads to a lack of adherence, worsening the overall disease state. The challenge for physicians is to identify patients who have low awareness of their disease and prescribe a treatment that is easy for them to adhere to. This could improve both their negative and positive symptoms, decrease recurrence of anti-psychotic episodes and improve overall quality of life for those suffering with schizophrenia.

PATIENT PROFILE

All patients receiving orals
(n=3778)

All patients receiving LAIs
(n=2204)

Adherence

Fully adherent: 72%
Partially adherent: 34%
Non-adherent: 4%

Fully adherent: 78%
Partially adherent: 28%
Non-adherent: 6%

Level of insight

Fully aware: 42%
Moderately aware: 44%
Fully unaware: 13%

Fully aware: 29%
Moderately aware: 51%
Fully unaware: 20%

First line therapy

29%

18%

¹ Schizophrenia Treatment Landscape Study, Lundbeck, 2012

The brain foundation

Seventy percent of Lundbeck is owned by the Lundbeck Foundation. What does the Foundation do and what does it mean for Lundbeck, its patients and neuroscience at large?

Back in 1954, Grete Lundbeck, the widow of Lundbeck's founder Hans Lundbeck, established the Lundbeck Foundation by donating a large amount of her shares and willing the rest to the Foundation. A visionary move, the goal was to ensure a clear purpose and governance for the future of the company.

The Lundbeck Foundation today

Today the Lundbeck Foundation owns 70% of Lundbeck and the two organizations remain completely independent. Lundbeck is an individual entity, listed on the Copenhagen stock exchange, with its own governance structure and its own executive management and board of directors. Yet the two organizations share a vision to drive progress in neuroscience and give back to local and global communities.

The CEO of the Lundbeck Foundation, Lene Skole says, "We are an industrial foundation, which means we are a combination of a business and a charity. We do not have owners, and income from our commercial activities – usually dividends from the companies we own – is channeled back into society through donations for various purposes."

The Lundbeck Foundation is a majority shareholder in two other Danish companies: ALK, a pharmaceutical company focusing on the prevention and treatment of allergies; and Falck, a service provider within emergency, safety and healthcare. All three companies are subsidiaries of the Foundation.

Broad investments

The Foundation also has investments in around 20 life science companies in the US and Europe through its venture activities. Lundbeckfonden Ventures is an international evergreen venture fund with an ongoing investment frame of DKK 1.6 billion to invest in life science companies. Lundbeckfonden Ventures focuses on the development of new treatments that address unmet medical needs – particularly pharma products and technology platforms that are close to or in clinical development.

"We manage around 14 billion Danish kroner in free assets, of which a large part is invested in listed equities," Lene Skole says. "Our investment focus is not limited to life sciences. In fact, our portfolio is quite diverse, covering everything from luxury goods to Chinese technologies. This secures sufficient reserves to maintain a stable level of grant activities and support our subsidiaries, if necessary."

Lundbeck and the Lundbeck Foundation share more than just the name and dividends. They also share the commitment to neuroscience.



INVESTMENTS IN NEUROSCIENCE

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Committed to the brain

Lundbeck and the Lundbeck Foundation share more than just the name and dividends.

They also share the commitment to neuroscience: "We want to be known as 'the brain foundation' and we want Denmark to become one of the strongest brain research nations in the world. Just like Lundbeck, we are committed to the brain," says Lene Skole.

Each year, the Foundation awards around half a billion Danish kroner in biomedical research grants. Some of these are dedicated to

funding of science teaching and science communications projects. In 2016, the Foundation's grants corresponded to 718 full-time researchers and other scientific staff at Danish universities. "The brain is the least explored part of the body, even though one in three Europeans suffers from a brain disease. We believe the brain deserves a lot of attention, so at least half of our grants are dedicated to the brain." The Lundbeck Foundation is the largest private donor to neuroscience in Denmark, with DKK 1.6 billion going to brain-related research from 2010 to 2016.

What does the Foundation mean to Lundbeck?

The combination of being largely owned by a foundation and at the same time being listed on the stock exchange means a lot to Lundbeck. "Our job is to invent and bring innovative treatments to patients and hereby create value for patients, society and not least our shareholders," says Anders Götzsche, interim CEO of Lundbeck. "Foundation ownership gives stability in times of prosperity as well as recession. On the other hand, the listing keeps us on our toes,"



he says. "The foundation model is unique and an immense benefit to Danish companies and the Danish economy. All successful companies are obvious targets for major international groups – and they will be bought up if they don't have an owner that protects them. Being owned by a foundation brings confidence."



The largest Lundbeck Foundation grant in history: iPsych

The Foundation awarded DKK 240 million to a group of world-class Danish scientists working to find the causes of psychological disorders, in order to develop better and personalized therapies in the future.

The members of the project team are (from the left): Professor Anders Børghlum, Professor Ole Mors, both from Aarhus University Hospital, David Hougaard, Head of Department at Statens Seruminstitut (SSI), Professor Preben Bo Mortensen, Aarhus University, Professor Merete Nordentoft and Professor Thomas Werge, Mental Health Services – Capital Region of Denmark.



The most prestigious neuroscience research prize in the world: The Brain Prize

A prize of € 1 million is awarded to leading international brain researchers who have had a ground-breaking impact on neuroscience. In 2017, the winners were three professors from Ireland, UK and Germany (all based in the UK). They received the Brain Prize for their multidisciplinary analysis of brain mechanisms that link learning to reward, which has far-reaching implications for the understanding of human behaviour, including disorders of decision-making in conditions such as gambling, drug addiction, compulsive behaviour and schizophrenia.

Lundbeck in brief



We are focused, passionate and responsible in everything that we do, and we work determinedly to meet patients' needs for those living with depression, schizophrenia, Parkinson's disease and Alzheimer's disease. Our 5,000 skilled employees in more than 50 countries embody Lundbeck's unique culture, which since **Lundbeck was established in 1915 in Copenhagen** has been built on innovation, globalization and profitability.

For more than 70 years, we have been at the forefront of neuroscience research. We are fascinated by the brain and are **experts in psychiatric and neurological disorders**. We work closely with strategic partners all over the world, ensuring the best possible foundation for innovation and the development of new treatment solutions.



Our largest shareholder is the **Lundbeck Foundation** which holds approximately 70% of the shares. The Foundation was established in 1954 with the purpose of ensuring stability for Lundbeck and our business activities. The Foundation annually **grants about DKK 500 million to support medical research** and educational and communication activities. Lundbeck and the Lundbeck Foundation share more than just the name and dividends. We also share the commitment to neuroscience.

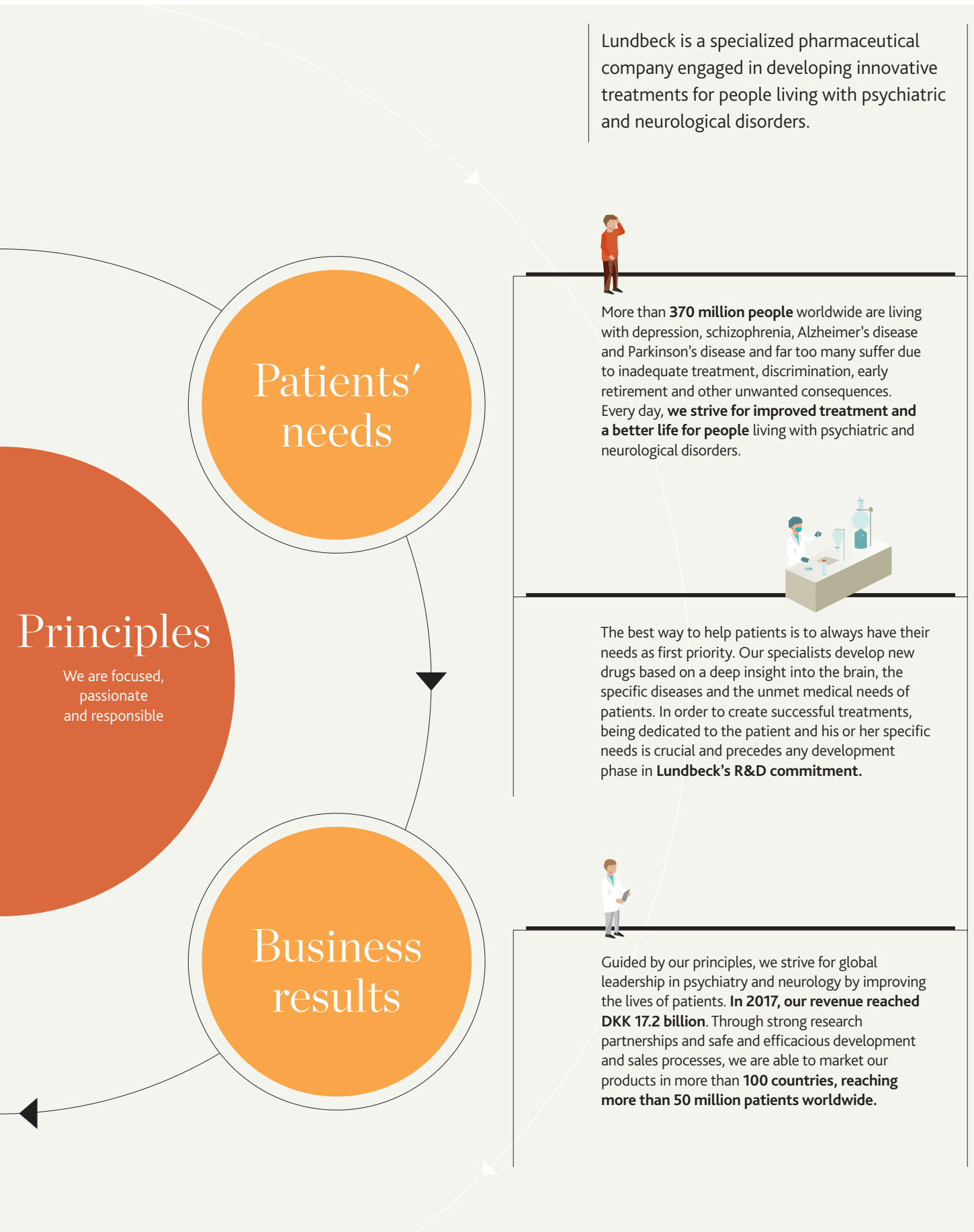


Innovation

Vision

We strive for global leadership in psychiatry and neurology by improving the lives of patients.

Shareholder value



“Parkinson’s will be with you for the rest of your life. So it’s important to think about how you want to deal with it. If you see it as your enemy, you will allow hatred into your mind and hurt yourself. Instead, try to treat Parkinson’s as you would a friend.”

Sheng Kanghua
Parkinson’s disease

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